

## Division of Clinical Pharmacology and Therapeutics

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### General Summary

The Division of Clinical Pharmacology and Therapeutics was established in July 1995. The aim of the division is to investigate drug treatment, mainly in the area of internal medicine, whereas other departments of clinical pharmacology in Japan focus on registration trials, particularly phase I trials. Because a clinical laboratory where we had performed many human pharmacological studies became unavailable in 2003, we shifted our research from human studies to multicenter clinical trials and pharmaco-epidemiological studies.

### Research Activities

We have performed a pharmacoepidemiological study of the prescription of antihypertensive drugs in patients with diabetes. Patients with hypertension complicated by diabetes are considered to be at high risk for cardiovascular events; therefore, the target blood pressure is set lower than for patients who have hypertension but no diabetes, and the drugs of choice are different. We investigated the use of antihypertensive drugs in patients who have hypertension with or without diabetes by means of prescription data from 3 university hospitals.

Statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) have been widely used to treat hyperlipidemia. They have adverse effects on muscle, the liver, kidneys, and other organs. To investigate the incidence of these adverse effects and antihyperlipidemic effects, we started a pilot study in 3 major hospitals, including our hospital, according to a case-cohort study design in which detailed data were collected in all cases and in a subcohort representing 5% of the whole sample. A full-scale study will be conducted with a large sample size of 20,000 to 30,000 patients.

An important issue for medicine in the 21st century is to identify patients who are responsive or unresponsive and those who show or do not show adverse reactions to drugs. We started a collaborative study with other institutions to examine the relationship between drug-metabolizing enzyme gene polymorphisms and drug effects in residents of an isolated island. We have analyzed the drug-metabolizing enzymes CYP2C9 and CYP2C19. Some of the results have already been applied to drug therapy.

An administrative office for registration trials was established in the hospital in February 1999, and the system for registration trials in the hospital has been reformed to meet the demands of the new good clinical practice (GCP) guidelines. Seven clinical research coordinators (CRCs)—6 nurses and 1 pharmacist—now facilitate clinical trials. The CRCs have started to help with both registration trials and investigator-initiated trials. CRCs were introduced into all registration trials since 2004; the quality and speed of these trials were much improved.

The Ministry of Health, Labour and Welfare started a New 5 Yearly Clinical Trial Action Plan to help registration trials to cope with trials performed abroad. This action plan selects 10 core hospitals and 30 major clinical trial institutions. The Jikei University Hospital applied to be a major clinical trial institution and was accepted. According to this plan, we reinforced CRCs and introduced data managers to improve the clinical trial system. We also introduced an information technology system for processing registration trial management.

## Publications

**Kamijima Y<sup>1</sup>, Ooba N<sup>1</sup>, Yagame M (Tokai Univ), Samizo K (Bosei Pharmacy), Shimodozono Y (Kagoshima Univ), Kageyama S, Horiguchi S<sup>1</sup>, Nagai R<sup>1</sup>, Kusunoki T (Jpn Soc Pharmacoe-  
pidemiol), Kubota K<sup>1</sup> (Tokyo Univ).** Hypertension management in diabetic patients: prescribing trends from 1999 to 2005 in three Japanese university hospitals. *Pharmacoe-  
pidemiol Drug Saf* 2008; **17**: 904-11.

**Irie S (Kyushu Clin Pharmacol Res Clin), Matsumura Y (Novo Nordisk Pharm), Zdravkovic M<sup>1</sup>, Jacobsen LV<sup>1</sup>, Kageyama S (Novo Nordisk A/S).** Tolerability, pharmacokinetics and pharmacodynamics of the once-daily human GLP-1 analog liraglutide in Japanese healthy subjects: a randomized, double-blind, placebo-controlled dose-escalation study. *Int J Clin Pharmacol*

*Ther* 2008; **46**: 273-9.

## Reviews and Books

**Kageyama S.** Thiazolidinedione derivatives (in Japanese). *Rinshoyakuri* 2009; **40**: 35-9.

**Kageyama S.** Scientific basis of clinical trials (in Japanese). In: Nakano S, et al, editors. Soyaku ikuyaku iryo staff no tame no rinshoshiken tekisutobukku (in Japanese). Tokyo: Medical Publications; 2009. p. 29-34.

**Watanabe H (Hamamatsu Univ), Kageyama S, Kurihara C (Natl Inst Radiol Sci).** Actual status of GCP investigations and future perspective: for solution of "over quality issue": Focused on comparison of Japan, US, EU regulations (in Japanese). *Rinsho Hyoka* 2008; **35**: 667-81.